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Algorithms For Treatment of Major Depressive Disorder: Efficacy and Cost-Effectiveness

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ABSTRACT

In spite of multiple new treatment options, chronic and treatment refractory courses still are a major challenge in the treatment of depression. Providing algorithm-guided antidepressant treatments is considered an important strategy to optimize treatment delivery and avoid or overcome treatment-resistant courses of major depressive disorder (MDD). The clinical benefits of algorithms in the treatment of inpatients with MDD have been investigated in large-scale, randomized controlled trials. Results showed that a stepwise treatment regimen (algorithm) with critical decision points at the end of each treatment step based on standardized and systematic measurements of response and an algorithm-guided decision-making process increases the chances of achieving remission and optimizes prescription behaviors for antidepressants. In conclusion, research in MDD revealed that systematic and structured treatment procedures, the diligent assessment of response at critical decision points, and timely dose and treatment type adjustments make the substantial difference in treatment outcomes between algorithm-guided treatment and treatment as usual.

Introduction

Major depressive disorder (MDD) is a common and debilitating mental health disorder, being the second largest cause of global disability [1]. In addition to the intensive utilization of the health care system and substantial costs, MDD is associated with more functional impairment than most chronic medical illnesses. Specifically, MDD is a severe affective disorder occurring in individuals of all ages and races, characterized by single or recurrent major depressive episodes of at least 2 weeks duration, although most episodes last considerably longer. The worldwide Global Burden of Disease study of the World Health Organization has shown variations by country and region, but patterns and trends for depressive

disorders are similar worldwide [2]. MDD can begin at any age, even in childhood and adolescence, but the mean age of onset of MDD has been estimated around the age of 30, and often it occurs in later life. Estimates reveal that 50–85 % of the patients who have an episode will have another episode of major depression [3].

The outcome for a single depressive episode that is treated according to standard procedures (involving pharmacotherapy and psychotherapy) is generally good and most patients return to normal functioning when the episode is over. However, MDD is associated with considerable morbidity and mortality when an initial episode of depression evolves into a recurrent and debilitating refractory or chronic illness with significant and pervasive impairments in psychosocial functioning. The likelihood of a recurrence increases with the number of previous depressive episodes and the severity of the current episode [4].

Since the late 1980s, considerable increases in the number of treatment strategies, including new, pharmacologically more selective antidepressants and potential medication combinations, have made the treatment of MDD more complex. In addition, wide variations in clinical practice procedures have been recognized in the treatment of depressed patients. MDD is frequently associated with treatment-resistant courses, particularly if full symptom remission is considered as the target of treatment efforts. Of depressed patients, 30–40 % do not respond to the first drug treatment trial in pivotal trials; over 50 % of nonresponders to the initial treatment also do not respond to a second, different treatment. Of those who do respond to the initial course of treatment, up to 50 % maintain residual symptoms with the risk of early relapse and chronicity [5].

Among many hypotheses of why there is such a high nonresponse to treatments, it has been suggested that inadequate and unsystematic treatment performance may be among the major contributors to unfavorable treatment outcomes in the treatment of MDD [6–8]. Apparent "treatment resistance" frequently results from inadequate dosages, too brief durations of treatment, or insufficient use of the available therapeutic repertoire. Only a minority of "treatment-resistant" patients have absolute resistance (i. e., do not respond to an adequate dose and duration of treatment). Rigorous treatment management may enhance outcomes. On the other hand, the probability of response to an antidepressant declines by a factor of approximately 15–20 % for each adequately delivered but failed drug treatment [9].

In attempts to improve the quality of care and clinical outcomes, as well as undesirable practice variations among clinicians, algorithms for the treatment of depression have been issued for primary care and psychiatric practitioners. Such treatment algorithms have been proposed in clinical medicine as effective means to offer optimal treatment and improved outcome for patients with severe illness.

This review article discusses the concepts of treatment algorithms for MDD and highlights the issues encountered in the development and implementation of algorithms as well as in their evaluation. It also reviews major controlled studies on the effects of algorithm-guided treatment of MDD, focusing on the Texas Medication Algorithm Project (TMAP), the Sequenced Treatment Alternatives to Relieve Depression (STAR * D) trial, and the German Algorithm Project (GAP).

What contrasts practice treatment guidelines from algorithms?

Most textbooks list treatment options relevant to the disorder being discussed. This listing is based on both evidence and clinical experience. Little is said about the nature and certainty of the evidence that supports the use of each treatment. The treatment options are rarely compared or contrasted, and there is no discussion of either the sequencing of specific treatments or the tactics (e. g., dose or duration of a treatment trial) recommended by which to implement optimally each option [6]. Clinical practice guidelines have been developed by professional societies to provide systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific clinical circumstances [10–12]. The development of clinical practice guidelines reflects the growing emphasis on evidence-based medicine. While practice guidelines typically present specific treatments and the scientific evidence to support the efficacy, safety, and tolerability of each treatment option, they do not usually recommend specific treatment sequences. They may (if evidence is available) suggest specific patient groups for which the treatment is recommended. Furthermore, practice guidelines typically limit recommendations to those supported by a distillation of scientific information instead of relying on expert opinion to make recommendations. Research evidence, however, typically lags behind or only partly addresses situations confronted by clinicians on a daily basis. Examples of practice guidelines for depression include those by the American Psychiatric Association [10, 11] and the World Federation of Societies of Biological Psychiatry [9, 13].

In contrast, algorithms are more specific than guidelines, as they often recommend specific treatments to be delivered in particular sequences. Algorithms are viewed as cognitive tools intended to assist, but not limit, clinical decision-making. Algorithms often specify the strategies (i. e., which treatments to use and in what order or sequence) and the tactics (i. e., how to implement each treatment strategy) of treatment. A treatment algorithm often provides a flow chart to specify the treatment steps to follow based on a patient's clinical status and prior treatment response. Algorithm recommendations often rely on both scientific evidence and clinical judgment. As with guidelines, however, algorithms can only provide group-based guidance. The clinician must be knowledgeable enough to adapt, modify, or ignore the recommendations for the specific patient being treated in order to optimize care. In fact, since algorithm recommendations are even more specific than guideline recommendations (e. g., specifying the starting dose and rate of dose adjustment), there is an even greater need for sophisticated basic and clinical knowledge and for substantial clinical experience in the algorithm user to ensure the safe and proper adaptation of recommendations to individual patients [6, 14].

Procedures in treatment algorithms

The assumption underlying the development of systematic treatment approaches is that decreasing inappropriate variance and increasing the appropriate treatment strategy selection and tactical implementation should enhance patient outcomes, reduce apparent treatment resistance, increase the quality of care, and poten-

tially decrease direct and indirect costs of health care [14, 15]. Treatment algorithms provide a framework for clinical decision-making that allows multiple clinicians serving the same patient to provide consistent care over time and avoid inefficient, inadequate, or inconsistent medical decisions. If effective, algorithms or guidelines should produce (1) more rapid responses, (2) more complete responses (e. g., greater remission rates, better functional improvement), (3) reduce patient attrition, and/or (4) lower side effect burden for more patients than usual care. Treatment algorithms also offer a way of comparing and evaluating different treatment steps or sequences against a set standard to define which sequence is most effective for individual patients. Furthermore, algorithms provide a standardized reference framework for health economic calculations.

Treatment algorithms provide 3 types of guidance: (1) strategies (what treatments to use), (2) tactics (how to implement and tailor the chosen treatment strategy), and (3) treatment steps (in what order to implement the different treatment strategies). Typically, algorithms recommend a predefined goal (e. g., remission or response), as well as clinical methods or instruments by which to adjust and assess the results of each treatment (e. g., symptom and side effect rating scales). They also define critical decision points in the course of treatment when the results of a certain treatment are to be assessed, and based on this assessment, they recommend specific treatment revisions according to preset "if-then rules."

In clinical practice, treatment algorithms should be embedded in a multifaceted disease management (or collaborative care) program. Such programs generally incorporate a systematic treatment approach (e. g., evidence-based practice guidelines or algorithm-guided treatment regimens), patient/family education programs, practice reorganization to meet the needs of chronically ill patients, and available expert consultation for practitioners and staff.

Examples of multisite algorithm trials

TMAP

The first formal study to evaluate a chronic disease management program, including guided medication treatment algorithms, in psychiatric outpatients with schizophrenia, bipolar disorder, or MDD treated in the public mental health sector was the TMAP. The interventions included specific medication treatment algorithms [15–17], the regular systematic assessment of symptoms and side effects at each medication visit, the provision of a patient/family educational program [18], and the provision of additional staff to provide more frequent visits, closer follow-up of patients, patient/family education, and to guide physicians in implementation of the medication algorithms. For depressed patients, response to each treatment step was assessed by the 30-item Inventory of Depressive Symptomatology, Clinician Rating (IDS-C30) and Self-Report ($IDS\text{-}SR_{30}$) [19–21]. For MDD, the study design included a matched clinic comparison with 4 clinics providing the algorithm package, 6 clinics offering treatment as usual (TAU) only, and 4 clinics providing TAU for patients with MDD, but which also provided the algorithm package for the other disorders (either schizophrenic or bipolar disorder).

Results revealed a substantial clinically and statistically greater benefit in terms of depressive symptoms, function, and side effect burden for the algorithm group (n = 175) as compared to TAU (n = 175) [17]. The greatest effects were seen after 3 months of treatment ($IDS\text{-}C_{30}$ ALGO: − 8.59 / TAU: − 4.17; p = 0.002). Both groups continued to improve over the year, and the algorithm group continued to sustain its advantage over TAU. Preliminary analyses suggested that poorer adherence to the medication algorithm by providers was associated with poorer clinical outcomes.

STAR * D

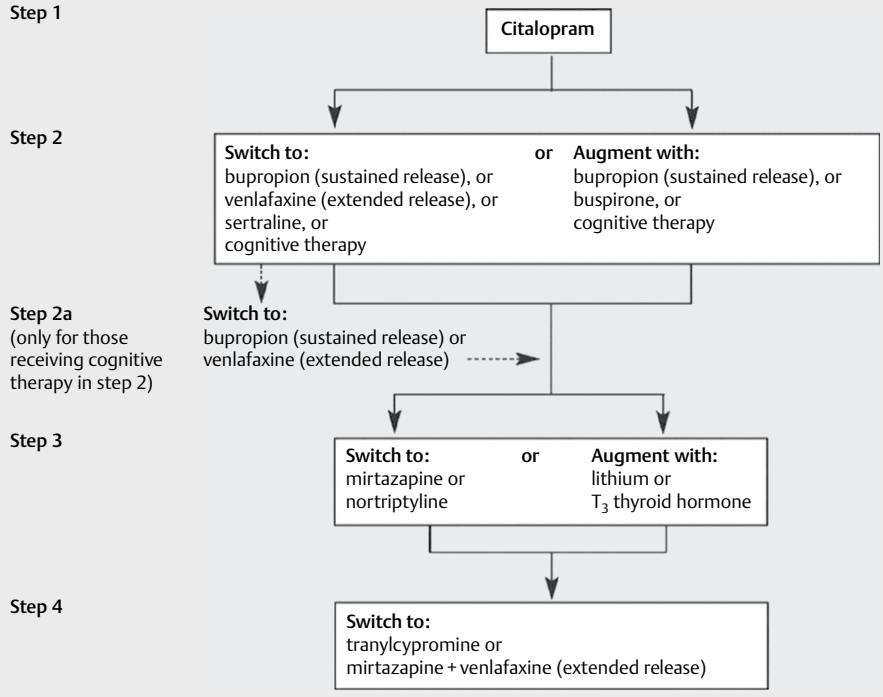
STAR * D (www.star-d.org) was a multisite trial in the United States (sponsored by the National Institute of Mental Health) conducted between 2000 and 2004 and included both primary and mental health care settings serving both public and private sector clients. The study aimed at defining prospectively which of several treatments are most effective for outpatients with nonpsychotic MDD with an unsatisfactory clinical benefit from an initial and, if necessary, subsequent treatment(s) [22, 23]. STAR * D is to date the largest prospective clinical trial of major depressive disorder ever conducted: in the nationwide association of 14 university-based regional centers, which oversaw a total of 23 participating psychiatric clinics and 18 primary care clinics, a total of 4041 patients were enrolled.

Specifically, the STAR * D identified a representative sample of depressed outpatients who were not initially treatment resistant. Following the first step in which all patients received citalopram, those without remission could receive up to 4 more treatments in 3 more treatment steps, with randomization at each step including both switch and augmentation options.

Treatment at each step was to last at least 12 weeks, but a triage option was offered for those who had achieved minimal benefit (< 15 % by week 6 or < 25 % by week 9) (▶ **Fig. 1**). Within the treatment levels physicians and patients could accept randomization to both or select either the switch or augmentation pathways, including cognitive therapy in the second step. At least 2 specific treatments (e. g., lithium and T3 augmentation) were included within the switch options and within the augmentation options at each step. Those who achieved remission (assessed with the 16-item Quick Inventory of Depressive Symptomatology, Clinician Rating [$QIDS\text{-}C_{16}$] < 5) entered the 12-month naturalistic follow-up phase, as could those with at least a response (> 50 % reduction in baseline $QIDS\text{-}C_{16}$ total score) (if they so choose).

Step 1

All enrolled patients began on a standard dose (20 mg/day) of a single selective serotonin reuptake inhibitor (SSRI) (citalopram) and were managed by clinic physicians, who followed an algorithm-guided acute phase treatment over a 12-week period. Medication dosing focused on maximizing the tolerable dose; if patients who were tolerating a medication had not achieved remission (i. e., complete symptomatic recovery from the depressive episode) by any of the critical decision points (weeks 4, 6, and 9), the algorithm recommended increasing the dose. Participants with an adequate clinical response to citalopram, defined by at least a 50 % reduction in baseline symptom severity measured with the $QIDS\text{-}C_{16}$, entered a 12-month, naturalistic, follow-up phase.



▶ **Fig. 1** STAR * D treatment steps.

On average, patients required nearly 7 weeks of measurement-based care to achieve remission. Notably, approximately half of the patients who ultimately remitted did so after 6 weeks, and 40 % of those who achieved remission required 8 or more weeks to do so.

Steps 2 and 3

Patients whose depressions did not remit after treatment in step 1 were able to participate in a sequence of up to 3 randomized clinical trials or steps. For example, at the end of step 1, patients whose depression had not fully recovered were eligible to participate in step 2. To reflect treatment decisions in clinical practice, patients were allowed to choose among acceptable options (e. g., to switch to a different treatment or augment the current treatment with another treatment). Participants could opt out of certain strategies as long as there were at least 2 possible options to which they might be randomly assigned.

Both steps 2 and 3 employed an equipoise stratified randomized design [24, 25], which was developed for STAR * D to mirror typical practice procedures. This design allowed patients to patients and clinicians to exclude themselves from being randomized to certain strategies or treatments, thereby reflecting more closely actual practice while retaining randomized comparisons. Thus, for example, a patient might want to switch treatments after step 1 (citalopram) has produced little benefit, but they might not want to risk being randomized to cognitive therapy. Thus, they could opt out of CT but had to agree to the 3 switch treatments to continue in the study [26], or they could opt out of switch options, but they had to accept all of the medication augmentation options [27]. This was designed to maximize patient retention in each of the treatment steps by respecting patients' preferences while ensuring randomization.

Overall, results from both steps 2 and 3 indicated that the augmentation options as well as the switch options were not different, though a direct comparison between augmentation and switch overall could not be made as most patients wanted to either switch or be augmented. Only a minority were willing to accept both these strategies at any step (2,3) As for specific medications at the second step, results suggested that either a within-class switch (e. g., citalopram to sertraline) or an out-of-class switch (e. g., citalopram to bupropion-SR) is effective, as was a switch to a dual-action agent (e. g., venlafaxine-XR). Furthermore, after 2 consecutive unsuccessful antidepressant trials, a change in pharmacologic mechanism did not affect the likelihood of remission. The third treatment step was associated with only a 15 % remission rate as compared to 33 % and 27 % in steps 1 and 2, respectively. Over the course of the 4 steps of treatment, the cumulative remission rate was only 67 % (not accounting for dropouts).

In general, remission rates in the study clinics were lower than expected, suggesting the need for several steps to achieve remission for most patients. There was no clear advantage for a single medication for patients whose depression did not remit after 1 or more aggressive medication trials. Both switching and augmentation steps appeared to be reasonable options when an initial antidepressant treatment failed, although these 2 strategies could not be directly compared. Further, the likelihood of remission after 2 vigorous medication trials substantially decreased, and remission would likely require more complicated medication regimens for which the existing evidence base is quite thin [5]. Finally, the failure to achieve remission and the greater number of failed acute

treatment trials before entering follow-up both contributed to a risk of relapse [5, 25].

The GAP

The GAP was initiated in the early 1990s to study the feasibility and efficacy of treatment algorithms in clinical practice focusing on depression treatment in psychiatric inpatient settings. Designed as a multistep project, it included 3 phases: GAP 1–3. Briefly, GAP 1 was an observational 2-year pilot study to evaluate effectiveness, feasibility, and acceptance among algorithm users [28]. GAP 2 was a randomized, controlled, single-center study to evaluate treatment efficacy and treatment process compared to TAU [29]. Finally, GAP 3 was a nationwide, randomized, controlled study to evaluate efficacy of 2 different treatment algorithms compared to TAU [30]. GAP 3 was conducted as a multisite project within the "Research Network on Depression" (Kompetenznetz Depression) supported by the German Federal Ministry for Education and Research.

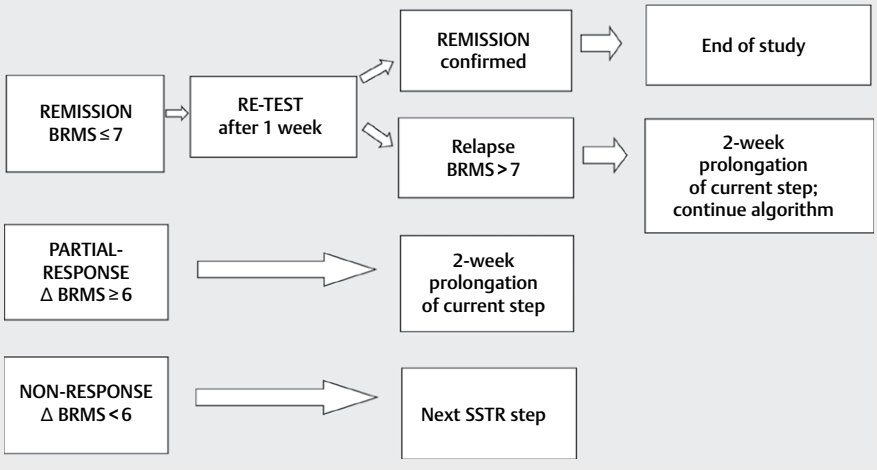
GAP 1

Phase 1 of GAP was an observational 2-year single-center pilot study to evaluate the effectiveness, feasibility, and acceptance of a standard stepwise drug treatment regimen (SSTR) for inpatients with a major depressive episode [28, 31]. The algorithm comprised up to 5 sequential treatment steps (step 0: taper previous antidepressant medication; step 1: antidepressant monotherapy, including high-dose treatment; step 2: augmentation with lithium; step 3: switch to the irreversible monoamine oxidase inhibitor tranylcypromine; step 4: switch to electroconvulsive therapy). The primary feature of the SSTR algorithm is a stepwise treatment change based on the results of clinical evaluations with the Bech-Rafaelsen Melancholia Scale (BRMS) [32] at the end of each treatment step. A total of 119 (out of 348 eligible) depressed patients were enrolled in the study, indicating a moderate acceptance of the antidepressive treatment algorithm by physicians who were not specifically trained in the algorithm. GAP 1 demonstrated favorable overall clinical effectiveness of algorithm-guided treatment of depression (total response rate: 72 %) and a moderate acceptance by algorithm-naïve physicians (patient inclusion rate: 48 %). An intent-to-treat analysis showed that 38 % of enrolled patients achieved remission (BRMS < 7) [32], while another 34 % achieved response (Δ BRMS > 50 %) without remission. It was concluded that algorithm-guided antidepressive treatment showed a favorable response rate in those depressed patients who were treated according to the SSTR protocol but users would need to be trained in applying treatment algorithms to ensure acceptance.

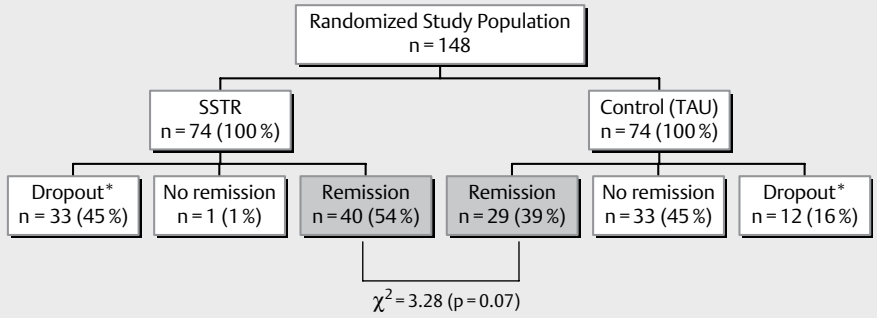
GAP 2

Phase 2 (1997–2000) of GAP was a randomized, controlled, single-center study to evaluate treatment efficacy and treatment processes with SSTR as compared to standard TAU in 148 inpatients [29]. The ALGO regimen included sleep deprivation, antidepressant monotherapy, lithium augmentation, monoamine oxidase inhibitor therapy, or electroconvulsive therapy guided by scores on the clinician-rated BRMS. The clinical outcome was categorized as nonresponse (change in BRMS < 6), partial response (change in BRMS ≥ 6 but total score > 7) or remission (BRMS ≤ 7) At critical decision points, categorization resulted in specific therapeutic action. Nonresponse after completion of the current step led to the next step; partial response led to an extension of the current step for another 2 weeks. No step, however, could be extended more than once. In cases of persistent partial responses at the next critical decision point, a switch to the next treatment step was mandatory. Remitted patients remained at the current step and were reevaluated after 1 week. If remission was confirmed, the patient exited the study and could be discharged. If remission could not be confirmed, the SSTR continued with a 2-week prolongation of the current step (▶ **Fig. 2**). The primary outcome was time to remission; secondary outcomes were remission rates, number of changes in treatment strategies (types), and the number of different prescribed medications over the treatment period.

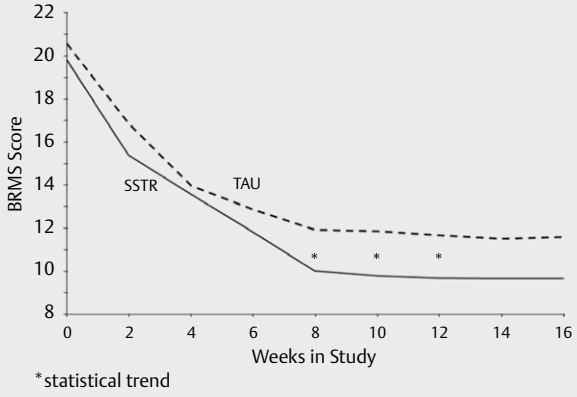
Although more patients dropped out of the SSTR group (33 of SSTR; 12 of TAU), the probability of remission tended to be higher in SSTR (▶ **Fig. 3**). Survival analysis (intention-to-treat analysis) revealed that SSTR patients had a 2-fold probability of achieving remission as compared to TAU patients (HR 2.0; p = 0.004). ▶ **Fig. 4** demonstrates the decline of depression scores on the BRMS in the



▶ **Fig. 2** The GAP studies: Flowchart of algorithm-guided medical decision making; BRMS = Bech-Rafaelsen Melancholia Scale.



▶ **Fig. 3** Randomization assignments, remission and dropout rate of the GAP 2 study.



▶ **Fig. 4** GAP 2 Study: Decline of depression scores on the Bech-Rafaelsen Melancholia Scale (BRMS) in the SSTR (n=74) vs. control group (TAU) (n=74) over time.

SSTR (n = 74) vs control group (TAU) (n = 74) over time. Compared to remitters in the SSTR group, the number of strategy changes to achieve remission was significantly higher in TAU remitters (3.0 vs. 1.0) and had more psychotropic medications (fix and optional agents, parallel or sequential combination of different psychotropics). The authors concluded that this study revealed better outcomes for algorithm-guided treatment and less frequent medication changes than TAU treatment.

GAP 3

Phase 3 of GAP (2000–2005) was a multicenter, randomized, controlled inpatient study supported by the German Federal Ministry for Education and Research and conducted by the "German Research Network on Depression" [30, 33]. This study evaluated treatment efficacy and efficiency of 2 different methods to deliver algorithms (1: ALGO; 2: computerized documentation and expert system [CDES]) compared to TAU. Three treatment groups were included within the ALGO group that included different "second-step-strategies" (a: lithium augmentation; b: dose escalation; c: switch to another antidepressant medication) in patients nonresponsive to a 4-week monotherapy. CDES was a software that linked individual response data of a patient to a probability matrix. Depending on the patient's probability of responding or not responding to current treatment, it proposed either continuing or changing the present strategy with regard to the patient's individual medication record but without providing explicit recommendations.

Inpatients with a major depressive episode, aged 18–70 years from 10 psychiatric hospitals, were randomized to 5 different treatment arms, 3 of which were standardized stepwise drug treatment algorithms (ALGO). The fourth arm proposed medications and provided less specific recommendations to maintain or change the current strategy based on a CDES. The fifth arm received TAU. ALGO included 3 different second step strategies for nonresponders to the initial 4-week antidepressant monotherapy. The second steps were lithium augmentation (ALGO LA), antidepressant dose-escalation (ALGO DE) or switch to a different antidepressant (ALGO SW). Time to remission (HAMD-21 < 9 collected by nonblind raters) was the primary outcome. Time to remission was significantly shorter for ALGO DE (n = 91) compared to both TAU (n = 84) (HR = 1.67; p = 0.014) and CDES (n = 79) (HR = 1.59; p = 0.031) and ALGO SW (n = 89) compared to both TAU (HR = 1.64; p = 0.018) and CDES (HR = 1.56; p = 0.038). For both ALGO LA (n = 86) and ALGO DE, fewer antidepressant medications were needed to achieve remission than for CDES or TAU (p < 0.001). Remission rates at discharge differed across groups; ALGO DE had the highest rates (89.2 %) and TAU had the lowest rates (66.2 %) [30]. In conclusion, in this multisite controlled study algorithm-based procedures increased the efficacy of applied treatments in the care of depressed in patients as opposed to TAU and to an individualized software-based algorithm.

Does algorithm-guided treatment of depression reduce treatment costs?

Because MDDs belong to the major health burdens to societies, an economic perspective in the evaluation of health care and distribution of resources most effectively is of high importance. Globally, the effect of depression on aggregate economic output is predicted to be USD $5.36 trillion between 2011 and 2030, and reduction of these substantial costs is a key objective for all countries [34]. A look into costs of depression in Germany demonstrates the

economic magnitude of the problem: with €1.6 million more than 50 % of the direct treatment costs of depression (€1.6 million per year) are caused by inpatient care. Eighty percent of the direct treatment costs are caused by only 10 % of the patients [35].

To find out if algorithm-guided treatment of depression may reduce costs, a health economic evaluation of data from the GAP 2 study [29], including a cost effectiveness analysis (CEA), was performed [36]. Direct treatment costs were calculated by daily hospital charges and medication costs per patient. CEA was conducted as follows: average direct treatment costs over remission-rate per treatment group resulting in expended cost per remitted patient. Treatment costs in the ALGO group were significantly lower compared to TAU (€10,830 (± €8,632); €15,202 (± €12,483); p = 0.026). The CEA revealed that the costs per remission in TAU were approximately twice as high as in SSTR (SSTR: €20,055; SSTR: €38,981). The CEA of medication costs that represent only a small proportion of total inpatient treatment costs also showed a superior cost effectiveness. This pilot study demonstrated that algorithm-guided treatment was associated with significantly lower health care costs and superior cost effectiveness as compared to TAU.

In a follow-up study, findings from this pilot study with data from the multicenter GAP 3 study were replicated. Treatment costs were calculated for 2 time periods: the study period (from enrolment to exit from study) and time in hospital (from enrolment to hospital discharge) based on daily hospital charges. Cost per remitted patient was calculated; indirect costs were not assessed [37]. For the study period, ALGO costs were significantly lower than TAU (ALGO: €7848; TAU: €10,033; p = 0.04). For time in hospital, costs were not different. Remission rates were greater in ALGO (83.3 %) than TAU (66.2 %) for time in hospital (p = 0.002); cost per remission was lower in ALGO (€13,554) than TAU (€20,066) for the study period (p < 0.000) and for time in hospital (ALGO: €17,582; TAU: €21,516; p = 0.036).

In summary, in 2 independent studies, it was found that treatment algorithms reduce direct costs for treatment and enhance the cost effectiveness of the care of depressed patients. Implementation of treatment algorithms in inpatient care can help minimizing treatment costs.

Components of success in algorithm-based treatment

Studies of treatment algorithms have included 2 different but potentially active elements that could contribute to their apparent effectiveness: the specific treatments used at each step and the highly structured approach to monitoring the results of the treatment and to consequently adjusting or fine-tuning the treatment. Specifically, with respect to the latter element, the assessment of symptomatic outcomes at each visit, frequent enough visits, and the regular measurement of side effects may lead algorithm-guided clinicians to more vigorously dose the medications, more diligently manage side effects, and, therefore, be more likely to conduct trials of adequate but not excessively prolonged durations, as well as to recognize when full remission or maximal benefit has not been obtained and to adjust or change the treatment. Evidence to support this notion comes from the GAP 2 study that revealed that the applied treatment strategies under which remission was achieved did not differ for the TAU and algorithm groups. Rather, the method of treatment execution differed. Analyses of only patients who remitted in both groups found significantly fewer treatments being used and less frequent use of polypharmacy in the algorithm group as compared to TAU [29]. In addition, in a single-site study in Beijing the procedures (measurement-based care with guideline- and rating scale-based decisions) without involving the specifics of an algorithm were compared to standard treatment (clinicians' choice decisions) with a substantial benefit for the measurement-based care group (time to and rates of response and remission rates and higher medication dosing without higher side effects) [38].

That diligent care is at least an essential part of the efficacy of algorithms is also supported by the collaborative care studies that demonstrate the benefit of a diligent, well-structured patient care with regard to clinical effectiveness as well as to patients' adherence compared to TAU [39].

Is there a preferred pathway?

Generalizability remains a major challenge in algorithm development and implementation. Tailoring algorithms to specific clinical situations or patients is a future goal. Without valid predictors (e. g., clinical, mechanistic or pharmacogenetic) of which treatment is preferred for specific patients, response heterogeneity among patients with MDD remains a major problem in performing and interpreting algorithm studies and in the implementation of guidelines in clinical practice. The treatment that seems suitable for an average study sample may not be the best for a particular patient in a specific clinical situation. Response patterns may substantially differ based on psychiatric comorbidities, severity, level of treatment resistance, chronicity, clinical subtype (e. g., melancholic, atypical, or seasonal features), and the presence of general medical conditions. When more concurrent axis I [5, 27, 40], axis II [41, 42], or axis III conditions [43–45] are present at baseline, remission may be less likely or it may take longer to achieve. Some evidence also suggests that longstanding, more chronic depressions will take longer to remit or are perhaps less likely to remit with various treatments [40, 46, 47].

Given the many different features that may affect the likelihood or time to benefit, the preferred algorithm-guided pathway for particular patients is not yet available. Clinical consensus and physicians' individual rational decision-making are obligatory elements to bridge the gaps when implementing and using algorithms in practice. Clinicians must be familiar with how to adapt an algorithm to specific clinical needs (e. g., moving the timing of the critical decision point in treatment resistant patients who may be expected to respond more slowly).

Conclusions and outlook

Chronic and treatment-resistant depressive disorders remain a significant problem in clinical practice in spite of an increase in the number of antidepressive treatment options and the development of new antidepressive compounds during the past 30 years. In fact,

mental health professionals increasingly observe patients with depressive disorders who do not respond adequately to drugs used as monotherapy or in combinations and, subsequently, develop a chronic course of the illness.

Although it might seem only too clear that treatment of depression ought to be performed in a diligent manner, the studies comparing algorithm-guided treatment with TAU suggest that it is the highly structured procedure of treatment and the operationalized assessment of response that makes the difference in treatment outcomes between both conditions. At least highly diligent treatment is not the usual treatment in today's clinical practice.

Evidence to date supports the following conclusions. First, it is possible to develop algorithms for the treatment of MDD. Second, these algorithms seem to provide better clinical outcomes than TAU when properly implemented. Third, the proper implementation of these algorithms requires the regular assessment of symptomatic outcomes achieved with each treatment step to reliably judge whether additional modifications of either treatment tactics (e. g., dose or duration) or strategy (type of treatment) is needed to optimally tailor the treatment to each patient in a process referred to as measurement-based care [48]. In addition, other modifications of routine practice procedures to either provide greater clinician-patient interaction or to install a chronic disease management program may be needed to enhance engagement and treatment adherence, reduce attrition, and enhance overall symptomatic and functional outcomes.

However, research on measurement-based care and algorithms have only just begun; many questions remain. Most importantly, we have a lack of randomized point of care trail evidence upon which to recommend one over another treatment after the first 1 or 2 treatment steps. The adoption and evaluation by systems of care or networks of practitioners of treatment algorithms that include randomization to different treatments after inadequate response to the first 2 treatment steps would be a cost-effective method by which to acquire this much-needed evidence. Further unsolved issues include the following. Is one algorithm preferred over another for all types of depressed patients or for specific subgroups? Is there some point after which additional changes in the treatment plans (e. g., additional efforts to augment or switch medications) are very unlikely to provide any additional benefits? What is the role of psychotherapy for depressed patients who are treated with medications? Can psychotherapy reduce the need for long-term medication in patients with chronic or recurrent forms of depression? Finally, with further work in the area of pharmacogenetics, one hopes that more valid and patient-specific treatment recommendations can be made.

As for economic considerations, algorithms may also decrease the direct cost of treatment to the treatment system, and they may reduce societal costs by increasing productivity, reducing disability, or even by prolonging life. Additional studies to assess whether and for which patients carefully implemented treatment algorithms are cost efficient are needed.

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